

## **IN THE SPECIFICATION**

Please amend the paragraph beginning on page 1, line 9, of the application to read as follows:

This application is a continuation application of application Serial No. 09/894798 filed June 28, 2001, and claims the benefit of U.S. provisional application Serial No. 60/349,310, filed January 15, 2002, which is incorporated herein by reference.

Please amend the paragraph on page 3 beginning at line 14 as follows:

Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline form in the solid state. A single molecule may give rise to a variety of crystal forms (also called “polymorphs,”[,] “hydrates,” or “solvates”) having distinct physical properties. [For a general review of polymorphs and the pharmaceutical applications of polymorphs see G.M. Wall, *Pharm Manuf.*, **3**] For a general review of polymorphs and the pharmaceutical applications of polymorphs see *Pharm Manuf.*, **3**, 33 (1986); J.K. Haleblan and W. McCrone, *J. Pharm. Sci.*, **58**, 911 (1969); and J.K. Haleblan, *J. Pharm. Sci.*, **64**, 1269 (1975), all of which are incorporated herein by reference.

Please amend the paragraph on page 10 beginning at line 19 as follows:

The dissolving step is optionally performed by heating crystalline carvedilol at a temperature from about 50° C [0] to about 60° C for about 6 hours.

Please amend the paragraph on page 11 beginning at line 8 as follows:

The drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C [0] to about 60° C for about 6 hours.

Please amend the paragraph on page 12 beginning at line 10 as follows:

Optionally, the solvent mixture is selected from the group consisting of acetone:[  
]cyclohexane, chloroform:[ ]cyclohexane, dichloroethane:[ ]cyclohexane, dichloromethane:[  
]cyclohexane, pyridine:[ ]cyclohexane, [tetrahydrofuran] tetrahydrofuran:cyclohexane,  
dioxane:[ ]cyclohexane, acetone:[ ]hexane, chloroform:[ ]hexane, dichloroethane:[ ]hexane,  
dichloromethane:[ ]hexane, tetrahydrofuran:[ ]hexane and ethanol:[ ]hexane.

Please amend the paragraph on page 13 beginning at line 22 as follows:

An alternative embodiment of the present invention provides, forming the solvent solution containing carvedilol by dissolving carvedilol in an organic solvent and water and precipitating crystalline carvedilol Form III. In this embodiment the organic solvent is optionally an alcohol. The alcohol is preferably selected from the group consisting of methanol and ethanol. Alternatively, the organic solvent may be selected from the group of solvents consisting of pyridine, dioxane, and ethyl acetate and [tetrahydrofuran] tetrahydrofuran.

Please amend the paragraph on page 16 beginning at line 6 as follows:

The DTG thermal profile of Form IV is shown in Fig. 2. The differential scanning calorimetry (DSC) thermal profile of [form] Form III shows one melting peak around 100°\_C (96°\_C-110°\_C), depending on the samples and on the particle size. This melting peak is concomitant to a loss on drying of about 2% as measured by thermal gravimetric analysis (TGA). The amount of water in the sample as determined by Karl Fisher analysis is in good

agreement with the value obtained from TGA, thus confirming that the loss on drying is due to the dehydration of water, and indicating that this material is a hemihydrate.

Please amend the paragraph on page 16 beginning at line 21 as follows:

The DTG thermal profile of Form IV is shown in Fig. 4. The DSC thermal profile of [form] Form IV shows one melting peak at about 104°C.

Please amend the paragraph on page 17 beginning at line 6 h as follows:

The DTG thermal profile of Form V is shown in Fig. 6. The DSC thermal profile of Form V shows a solvent desorption endotherm[.] at about 67°C, followed by a recrystallization event, and a melting peak at 115°C. The desorption endotherm is concomitant to a loss on drying of about 14% as determined by TGA. This behavior is consistent with the loss of a molecule of MEK per molecule of carvedilol (the calculated stoichiometric value of mono-MEK is 15%).

Please amend the paragraph on page 20 beginning at line 10 as follows:

\_\_\_\_\_The resulting material is reslurried in ethylacetate (50[ml] mL) and water (20[ml] mL) containing 5% [Sodium] sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4[o]°C. Precipitated carvedilol was isolated by [filtration] filtration and crystallized from isopropanol.

The paragraph on page 20 beginning at line 23 has been amended as follows:

The resulting material is reslurried in ethyl\_ acetate (50[ml] mL) and water (20[ml] mL) containing 5% [Sodium] sodium carbonate until the pH reached 7.5. The organic phase was

separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4°C. Precipitated carvedilol was isolated by [filtration] filtration and crystallized from methanol.

Please amend the paragraph on page 21 beginning at line 5 as follows:

[Crystalline carvedilol is prepared according to the procedure in Example 3. The crystalline material is then dried at 50-60°C for 6 hours.] The dried crystalline carvedilol (220 g carvedilol) is dissolved in 2200 [ml] mL [Ehtyl Acetate] ethyl acetate. The ethyl acetate solution is heated with agitation to 77°C until the solid is [completly] completely dissolved. The ethyl acetate solution was then cooled with agitation to about 50°C in a time period of 15 minutes. [Te] The cooled solution was stirred for 48 hours. The solution was then cooled to 10°C in 0.75 hours with agitation. After stirring the suspension for additional 24 hours, the product was filtered. Pure Crystalline carvedilol Form I (170 g) was obtained.

Please amend the paragraph on page 21 beginning at line 16 as follows:

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table I. Carvedilol is crystallized by forming a solution of [carvidilol] carvedilol heated to reach a clear solution, usually close to the solvent boiling temperature. The solution is then cooled to ambient temperature and the precipitate is filtered to yield [Carvedilol for] carvedilol Form II.

Please amend Table I, on page 22 beginning at line 1, as follows:

**Table I**

| Solvent                                           | Ratio of Solvent ([ml]<br>mL):Carvedilol (g) |
|---------------------------------------------------|----------------------------------------------|
| Methanol                                          | 11                                           |
| Ethanol abs.                                      | 12                                           |
| 1-[propanol]Propanol                              | 14                                           |
| Isopropanol                                       | 13                                           |
| n-Butanol                                         | 11                                           |
| [Ethylen glycol]<br>Ethylene Glycol               | 13                                           |
| Ethyl-[acetate]Acetate                            | 10                                           |
| Butyl Acetate                                     | 12                                           |
| [isobutyl methl ketone]<br>Isobutyl Methyl Ketone | 12                                           |
| Dichloromethane                                   | 12                                           |
| Dichloroethane                                    | 25                                           |
| Acetonitile                                       | 50                                           |
| Acetone                                           | 25                                           |

Please amend the paragraph on page 22 beginning at line 21 as follows:

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table II. Carvedilol is crystallized by forming a solution of [carvidilol] carvedilol heated to about the solvent boiling temperature. The solution is then cooled to  $-20[ ]^{\circ}\text{C}$ , the precipitate is filtered and dried to yield [Carvedilol] carvedilol Form II.

Please amend Table II, on page 23 beginning at line 1, has been amended as follows:

**Table II**

| Solvent        | [Ratio of Solvent (ml):Carvedilol (g)<br>(Please Confirm Units)]<br>Ratio of Solvent (mL):Carvedilol (g) |
|----------------|----------------------------------------------------------------------------------------------------------|
| Isoamylalcohol | 50                                                                                                       |
| Toluene        | 53                                                                                                       |
| Xylene         | 51                                                                                                       |

Please amend the paragraph on page 23 beginning at line 10 as follows:

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the mixture of solvents listed in Table III. Carvedilol is crystallized by forming a solution of [carvidilol] carvedilol heated to form a clear solution, usually close to the boiling temperature of the mixture of solvent. The solution is then cooled to ambient temperature and filtered. The crystals are collected by filtration and dried to [yeld Carvedilol form] yield carvedilol Form II.

Please amend the paragraph on page 25 beginning at line 6 as follows:

Carvedilol (4\_g) was dissolved in 195\_mL mixture of water/methanol (in a ratio 1:3 respectively) by heating the mixture under stirring in 55°\_C water bath. The solution cooled to ambient temperature and left at ambient temperature without stirring for about 15 [h] hours, the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Please amend the paragraph on page 25 beginning at line 14 has follows:

Carvedilol (4\_g) was dissolved in 39\_mL pyridine by stirring at room temperature. 70 mL of water was then added dropwise until crystallization began. The solution was left at room temperature without stirring for about 80[h] hours, then the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield [Carvedilol] carvedilol Form III.